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Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: COMPOSITIONS AND METHODS FOR PREVENTION OF PHOTOAGING

(57) Abstract

Methods of preventing photoaging and other types of sun damage by topically applying a composition containing a serine protease inhibitor or milk are provided. Pharmaceutical compositions comprising serine protease inhibitors or milk for the prevention of photoaging and other types of sun damage are also provided.

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COMPOSITIONS AND METHODS FOR PREVENTION OF PHOTOAGING

BACKGROUND OF THE INVENTION

The effects of ultraviolet radiation from exposure to the sun on human skin are a growing concern for today's longer-lived population. The majority of changes associated with an aged appearance result from chronic sun-damage (Warren et al., *J. Am. Acad. Dermatol.*, 1991, 25:751-760; Frances, C. and Robert, L., *Int. J. Dermatol.*, 1984, 23:166-179). Dramatic alterations of the superficial dermis accompany the deep wrinkles and laxity common in photoaged skin. The major histopathologic alteration of photoaged skin is the accumulation of material which, on routine histopathologic examination, has the staining characteristics of elastin and is, thus, termed solar elastosis. Immunohistochemical staining has shown the poorly-formed fibers comprising solar elastosis to be composed of elastin (Chen et al., *J. Invest. Dermatol.*, 1986, 87:334-337; Mera et al., *Br. J. Dermatol.*, 1987, 117:21-27) fibrillin (Chen et al., *J. Invest. Dermatol.*, 1986, 87:334-337; Dahlback et al., *J. Invest. Dermatol.*, 1990, 94:284-291; Bernstein et al., *J. Invest. Dermatol.*, 1994, 103:182-186) and versican, the normal components of elastic fibers (Zimmerman et al., *J. Cell. Biol.*, 1994, 124:817-825). A coordinate increase in elastin, fibrillin and versican mRNAs has been demonstrated in fibroblasts derived from photodamaged skin, as compared to fibroblasts derived from normal skin from the same individuals (Bernstein et al., *J. Invest. Dermatol.*, 1994, 103:182-186). Elevated elastin mRNA levels in sun-damaged skin result from enhanced elastin promoter activity, as shown by transient transfections of fibroblasts with a DNA construct composed of the human elastin promoter linked to the chloramphenicol acetyltransferase (CAT) reporter gene (Bernstein et al., *J. Invest. Dermatol.*, 1994, 103:182-186).

Neutrophil elastase has been suggested to be an important mediator in the development of solar elastosis resulting from continued exposure to UVB (See Abstract from Ciba-Found. Symp., 1995, 192:338-46; discussion 346-7). Using an elastase-deficient hairless mouse model and specific small molecular weight elastase inhibitors, it has been shown that attenuation of neutrophil elastase activity results in a pronounced diminuation in the severity of UVB or chemically-induced skin tumors (Starcher et al. *J. Invest. Dermatol.*, 1996, 107:159-163).

A deficiency in alpha 1-antitrypsin has been suggested to allow proteases such as neutrophil elastase to destroy dermal elastin and, thus produce cutis laxa in Marshall's syndrome, a rare pediatric skin disease that is characterized by acquired localized neutrophilic dermatitis (Sweet's disease), followed by loss of elastic tissue in the dermis and cutis laxa (Hwang et al. *Arch. Dermatol.*, 1995, 131(10):1175-7). Alpha 1-proteinase inhibitor, also referred to herein as alpha 1-antitrypsin, is approved by the Food and Drug Administration as a plasma product for the treatment of hereditary alpha 1-antitrypsin deficiency. Alpha 1-antitrypsin has also been disclosed for use in the treatment of atopic dermatitis (Wachter, A.M. and Lezdey, J. *Annals of Allergy*, 1992, 69:407-414).

Alpha 1-antitrypsin is a member of the serine protease inhibitor (serpin) supergene family. Serpins are a superfamily of inhibitors involved in the mediation of a variety of biological processes essential to survival of a host. Members of the serpin family play a role in a great number of biological processes including, but not limited to, inflammation, fertilization, tumor migration, neurotropism, and heat shock. The serpin with the highest naturally occurring plasma concentration is alpha 1-antitrypsin. This serpin has activity toward both tryptic and chymotryptic proteases.

It has now been found that topical application of serine proteases such as alpha 1-antitrypsin prevents photoaging and other skin damage resulting from exposure to solar, and more specifically, ultraviolet radiation.

SUMMARY OF THE INVENTION

In the present invention, a new use is provided for serine proteases such as alpha 1-antitrypsin. It has now been demonstrated that topical application of alpha-1 antitrypsin protects against photoaging and other sun-damage such as sunburn and skin cancer caused by solar radiation. Accordingly, serine proteases with alpha 1-antitrypsin-like activities are believed to be useful as sunscreen agents. Compositions for use as sunscreen agents comprising serine proteases with alpha 1-antitrypsin like activities are also provided.

DETAILED DESCRIPTION OF THE INVENTION

Profound changes take place in the superficial dermis as a result of chronic sun-exposure. The major alteration is the deposition of massive amounts of abnormal elastic material, termed solar elastosis. It has been shown that solar elastosis is accompanied by elevations in elastin and fibrillin mRNAs and elastin promoter activity.

A transgenic mouse model which contains the human elastin promoter linked to a chloramphenicol acetyltransferase (CAT) reporter gene for testing compounds that may inhibit cutaneous photodamage has been developed. These mice express human elastin promoter activity in a tissue-specific and developmentally regulated manner. Promoter activity can be studied in this model as a function of small increases in ultraviolet radiation, demonstrating the sensitivity of the assay. In addition, quantitative data can be obtained after only a single exposure to ultraviolet radiation. A test compound is applied to the skin of a transgenic mouse capable

of expressing the human elastin promoter. The transgenic mouse is then exposed to solar radiation and human elastin promoter activity in the mouse is determined. The human elastin promoter activity is then compared to that in transgenic mice also exposed to an equivalent dose of solar radiation which were not treated with the test compound to determine whether or not the test compound provided protection against the solar radiation. Since elastin promoter activation is a primary event in cutaneous aging, these mice represent a mouse model of human photoaging.

Using this transgenic mouse line, the ability of alpha 1-antitrypsin to inhibit the effects of solar radiation on human elastin promoter activity was determined. Alpha 1-antitrypsin is produced in the milk of transgenic goats. Accordingly, in these experiments, 5 mice received either no treatment, 10 mice were treated with a 20 mg/ml solution of alpha 1-antitrypsin in goat's milk applied topically to the back, and 10 mice were treated with a solution of goat's milk alone applied topically to the back. A group of mice was also treated with saline only. Approximately fifteen minutes after application of the goat's milk containing alpha 1-antitrypsin, goat's milk alone, or saline these mice were exposed to 20 human minimal erythema doses (MEDs) of solar simulating radiation (SSR). Following phototreatment, the backs of the mice were rinsed twice with 70% isopropyl alcohol pads to remove any excess alpha 1-antitrypsin. This procedure was repeated over three consecutive days.

Mice were sacrificed and skin harvested for determination of CAT activity 24 hours after the third phototreatment. The baseline CAT activity of control mice receiving neither radiation nor alpha 1-antitrypsin was standardized to a value of one. Relative increases in CAT activity were 14.4 + 3.1 (mean + S.D.) in mice treated with goat's milk alone and 4.5 + 1.0 in mice treated with goat's milk containing alpha 1-antitrypsin. Thus, topical application of the serpin alpha 1-

antitrypsin produced a 69% reduction in CAT activity. In addition, it was found that milk alone provided 12% protection as compared to the saline control animals.

Accordingly, topical application of a composition comprising alpha 1-antitrypsin or other serpins with alpha 1-antitrypsin like activities to the skin provides protection against photoaging and other sun-damage such as sunburn and skin cancer. By "other serpins with alpha 1-antitrypsin-like activities", it is meant serine protease inhibitors with similar activity toward both tryptic and chymotryptic proteases as alpha 1-antitrypsin. Such serpins include both naturally occurring serine protease inhibitors and mutants rationally engineered to have similar activities and specificity to alpha 1-antitrypsin. Methods of rationally engineering serine proteases and their inhibitors are known. See, for example, Dang et al. *Nature Biotechnology*, 1997, 15:146-149.

Examples of compositions comprising a serpin with alpha 1-antitrypsin like activities include, but are not limited to creams, lotions and sprays. Methods of formulating serpins into creams, lotions and sprays as well as pharmaceutical additives for such formulations are well known to those skilled in the art. As will be obvious to those skilled in the art upon this disclosure, such compositions may further comprise secondary or additional sunscreens or free radical scavengers such as, but not limited to, Vitamin C and Vitamin E and analogs thereof. In a preferred embodiment, a composition comprising a serpin is applied to the skin prior to exposure to the sun. However, application of these compositions subsequent to the exposure can also mitigate any damage resulting to the skin from this exposure. It is believed that these compositions of the present invention will be especially useful in protecting individuals with heightened sensitivities to the sun, such as, but not limited to, individuals undergoing psoralen treatment for cancer, psoriasis and other skin conditions; individuals undergoing photodynamic therapy for

skin cancer, psoriasis and other skin conditions; individuals suffering from genetic repair defects such as xeroderma pigmentosa, albinism or other conditions resulting from decreased endogenous melanin pigment.

Further, as demonstrated herein topical application of a composition comprising milk or a product derived therefrom also provides protection against photoaging and other sun-damage such as sunburn and skin cancer. Accordingly, compositions such as creams, lotions and sprays which comprise milk or a product derived therefrom can also be formulated for use in protecting against photodamage and other sun-damage in normal individuals and those with a heightened sensitivity to the sun.

The following nonlimiting examples are provided to further illustrate the present invention.

EXAMPLES

Example 1: Transgenic mice expressing the human elastin promoter

A homozygous line of transgenic mice expressing the 5.2-kb human elastin promoter linked to a CAT reporter gene was used. Hsu-Wong et al., *J. Biol. Chem.*, 1994, 269:18072-18075. These mice express the human elastin promoter in a tissue-specific and developmentally regulated manner. Mice four or five days old were used since at this age, visible hair growth is not yet present.

Example 2: Solar Simulating Radiation

A Multiport Solar Simulator (Solar Light Company, Philadelphia, PA) containing a xenon arc lamp filtered through a Schott WG 320 filter (Schott Glaswerke, Mainz, Germany) was used to administer solar simulating radiation (SSR). The output of the solar simulator was measured by means of a 3D UV meter (Solar Light Company) and displayed as human minimal erythema doses (MEDs). The emission spectrum of the lamp

closely simulates solar radiation reaching the earth's surface. The light guides from the solar simulator were placed in light contact with the dorsal surface of the mice, which were restrained to prevent movement while SSR was administered. Unirradiated control mice were also restrained without receiving SSR.

Example 3: CAT Assay

To measure the expression of the human elastin promoter/CAT reporter gene construct in the skin of transgenic mice and in fibroblast cultures established from these animals, CAT activity was determined. For extraction of the CAT from skin, the specimens were homogenized in 0.25 Tris-HCl, pH 7.5, using a tissue homogenizer (Brinkmann Instruments, Inc. Westbury, NY). The homogenates were centrifuged at 10,000 X g for 15 minutes at 4°C and the protein concentration in the supernatant determined by a commercial protein assay kit (Bio-Rad Laboratories, Richmond, CA). Aliquots of the supernatant containing 100 μg of protein were used for assay of CAT activity by incubation with [^{14}C] chloramphenicol in accordance with well-known procedures. The acetylated and non-acetylated forms of radioactive chloramphenicol were separated by thin-layer chromatography and CAT activity was determined by the radioactivity in the acetylated forms as a percent of the total radioactivity in each sample.

What is Claimed:

1. A method of protecting humans exposed to sunlight against photoaging, sunburn and skin cancer comprising topically applying to skin of a human a serine protease inhibitor in an amount effective to protect the skin against photoaging, sunburn and skin cancer.

2. The method of claim 1 wherein the serine protease inhibitor is alpha 1-antitrypsin.

3. The method of claim 1 wherein the serine protease inhibitor is applied prior to exposure of the skin to sunlight.

4. The method of claim 1 wherein the serine protease inhibitor is applied subsequent to exposure of the skin to sunlight.

5. A method of protecting individuals with a heightened sensitivity to the sun from damage resulting from the sun comprising topically applying to the skin of an individuals with a heightened sensitivity to the sun a serine protease inhibitor prior to exposure of the individual to the sun.

6. The method of claim 5 wherein the serine protease inhibitor is alpha 1-antitrypsin.

7. A method of protecting humans exposed to sunlight against photoaging, sunburn and skin cancer comprising topically applying to skin of a human milk or a product derived from milk.

8. A pharmaceutical composition for prevention of photoaging and other sun-damage comprising a serine protease inhibitor, a second sunscreen or free radical scavenger, and a pharmaceutical additive.

9. The pharmaceutical composition of claim 7 wherein the serine protease inhibitor is alpha 1-antitrypsin.

10. A pharmaceutical composition for prevention of photoaging and other sun-damage comprising milk or a product derived therefrom and a pharmaceutical additive.

PCT/US00/04427

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 19 December 2000 (19.12.00)	
International application No. PCT/US00/04427	**Applicant's or agent's file reference** BERN-0032
International filing date (day/month/year) 22 February 2000 (22.02.00)	**Priority date** (day/month/year) 22 February 1999 (22.02.99)
Applicant BERNSTEIN, Eric, F.	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

13 September 2000 (13.09.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer F. Baechler
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

09/913697

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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To: JANE MASSEY LICATA
LAW OFFICES OF JANE MASSEY LICATA
66 E. MAIN STREET
MARLTON, NJ 08053

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Status Report ___
Docket Book ✓
N.P. 8434-01

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing *(day/month/year)*	20 JUN 2001
Applicant's or agent's file reference: BERN-0032	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/US00/04427	22 FEBRUARY 2000	22 FEBRUARY 1999

Applicant
BERNSTEIN, ERIC F.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	ZOHREH FAY
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

Form PCT/IPEA/416 (July 1992)*

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference BERN-0032	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US00/04427	International filing date *(day/month/year)* 22 FEBRUARY 2000	Priority date *(day/month/year)* 22 FEBRUARY 1999
International Patent Classification (IPC) or national classification and IPC IPC(7): A61K 37/00 and US Cl.: 514/21		
Applicant BERNSTEIN, ERIC F.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 3 sheets.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

   I ☒ Basis of the report

   II ☐ Priority

   III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability

   IV ☐ Lack of unity of invention

   V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

   VI ☐ Certain documents cited

   VII ☐ Certain defects in the international application

   VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
13 SEPTEMBER 2000	14 MAY 2001
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer ZOHREH FAY
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

Form PCT/IPEA/409 (cover sheet) (July 1998)★

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/04427

I. Basis of the report

1. With regard to the elements of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-7 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the claims:
pages 8-9 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the drawings:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the sequence listing part of the description:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[ ] contained in the international application in printed form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/~~fig~~ NONE

5. [ ] This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/04427

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	1-10	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-10	NO
Industrial Applicability (IA)	Claims	1-10	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claims 1-10 lack an inventive step under PCT Article 33(3) as being obvious over the chemical abstract 129:293666. The chemical Abstract teaches the use of alpha-1 antitrypsin as a phtoprotective agent against UVA exposure. In view of the above reference the claimed composition and the use thereof does not involve an inventive step .

---------- NEW CITATIONS ----------
NONE

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 26 JUN 2001
WIPO PCT

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
BERN-0032		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/04427	22 FEBRUARY 2000	22 FEBRUARY 1999
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Applicant BERNSTEIN, ERIC F.		

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Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

Form PCT/IPEA/409 (cover sheet) (July 1998)*

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International application No.
PCT/US00/04427

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pages NONE, filed with the demand
pages NONE, filed with the letter of _____

[X] the claims:
pages 8-9, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

[X] the drawings:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

[X] the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

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[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

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[X] the claims, Nos. NONE

[X] the drawings, sheets/~~fig~~ NONE

5. [ ] This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US00/04427

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	1-10	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-10	NO
Industrial Applicability (IA)	Claims	1-10	YES
	Claims	NONE	NO

2. citations and explanations (Rule 70.7)

Claims 1-10 lack an inventive step under PCT Article 33(3) as being obvious over the chemical abstract 129:293666. The chemical Abstract teaches the use of alpha-1 antitrypsin as a phtoprotective agent against UVA exposure. In view of the above reference the claimed composition and the use thereof does not involve an inventive step .

---------- NEW CITATIONS ----------
NONE

09/913697

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: JANE MASSEY LICATA
LAW OFFICES OF JANE MASSEY LICATA
66 E. MAIN STREET
MARLTON, NJ 08053

Docket System ✓
Status Report ✓
Docket Book ✓
4/5/01 ORC

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of Mailing *(day/month/year)*	05 MAR 2001
Applicant's or agent's file reference: BERN-0032	REPLY DUE within ONE months from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/04427	22 FEBRUARY 2000	22 FEBRUARY 1999

International Patent Classification (IPC) or both national classification and IPC
IPC(7): A61K 37/00 and US Cl.: 514/21

Applicant
BERNSTEIN, ERIC F.

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I [X] Basis of the opinion
- II [ ] Priority
- III [ ] Non-establishment of opinion with regard to novelty, inventive step or industrial applicability
- IV [ ] Lack of unity of invention
- V [X] Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI [ ] Certain documents cited
- VII [ ] Certain defects in the international application
- VIII [ ] Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).~~

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 *bis*.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 22 JUNE 2001

Name and mailing address of the IPEA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	ZOHREH FAY
Facsimile No. (703) 305-3230	Telephone No. (703) 308-1235

Form PCT/IPEA/408 (cover sheet) (July 1998) ★

WRITTEN OPINION

International application No.
PCT/US00/04427

I. Basis of the opinion

1. With regard to the **elements** of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-7 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the claims:
pages 8-9 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the drawings:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

[X] the sequence listing part of the description:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

[ ] contained in the international application in printed form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets ~~4/6~~ NONE

5. [ ] This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*

International application No.
PCT/US00/04427

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	1-10	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	NONE	YES
	Claims	1-10	NO
Industrial Applicability (IA)	Claims	1-10	YES
	Claims	NONE	NO

2. citations and explanations

Claims 1-10 lack an inventive step under PCT Article 33(3) as being obvious over the chemical abstract 129:293666. The chemical Abstract teaches the use of alpha-1 antitrypsin as a phtoprotective agent against UVA exposure. In view of the above reference the claimed composition and the use thereof does not involve an inventive step .

---------- NEW CITATIONS ----------

NONE

International application No.
PCT/US00/04427

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

TIME LIMIT:

The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.